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# Cognitive Vulnerability to Major Depression: View from the Intrinsic Network and Cross-network Interactions

Xiang Wang, MD, PhD, Dost Öngür, MD, PhD, Randy P. Auerbach, PhD, ABPP, and Shuqiao Yao, MD, PhD

**Abstract:** Although it is generally accepted that cognitive factors contribute to the pathogenesis of major depressive disorder (MDD), there are missing links between behavioral and biological models of depression. Nevertheless, research employing neuroimaging technologies has elucidated some of the neurobiological mechanisms related to cognitive-vulnerability factors, especially from a whole-brain, dynamic perspective. In this review, we integrate well-established cognitive-vulnerability factors for MDD and corresponding neural mechanisms in intrinsic networks using a dual-process framework. We propose that the dynamic alteration and imbalance among the intrinsic networks, both in the resting-state and the rest-task transition stages, contribute to the development of cognitive vulnerability and MDD. Specifically, we propose that abnormally increased resting-state default mode network (DMN) activity and connectivity (mainly in anterior DMN regions) contribute to the development of cognitive vulnerability. Furthermore, when subjects confront negative stimuli in the period of rest-to-task transition, the following three kinds of aberrant network interactions have been identified as facilitators of vulnerability and dysphoric mood, each through a different cognitive mechanism: DMN dominance over the central executive network (CEN), an impaired salience network-mediated switching between the DMN and CEN, and ineffective CEN modulation of the DMN. This focus on interrelated networks and brain-activity changes between rest and task states provides a neural-system perspective for future research on cognitive vulnerability and resilience, and may potentially guide the development of new intervention strategies for MDD.

**Keywords:** cognitive vulnerability, cross-network interaction, functional magnetic resonance imaging, intrinsic network, major depressive disorder

Major depressive disorder (MDD) is a common, recurrent, and severe psychiatric disorder and a leading source of disease burden,<sup>1</sup> with a lifetime prevalence of 16.2% in adults and a prevalence of 11.7%

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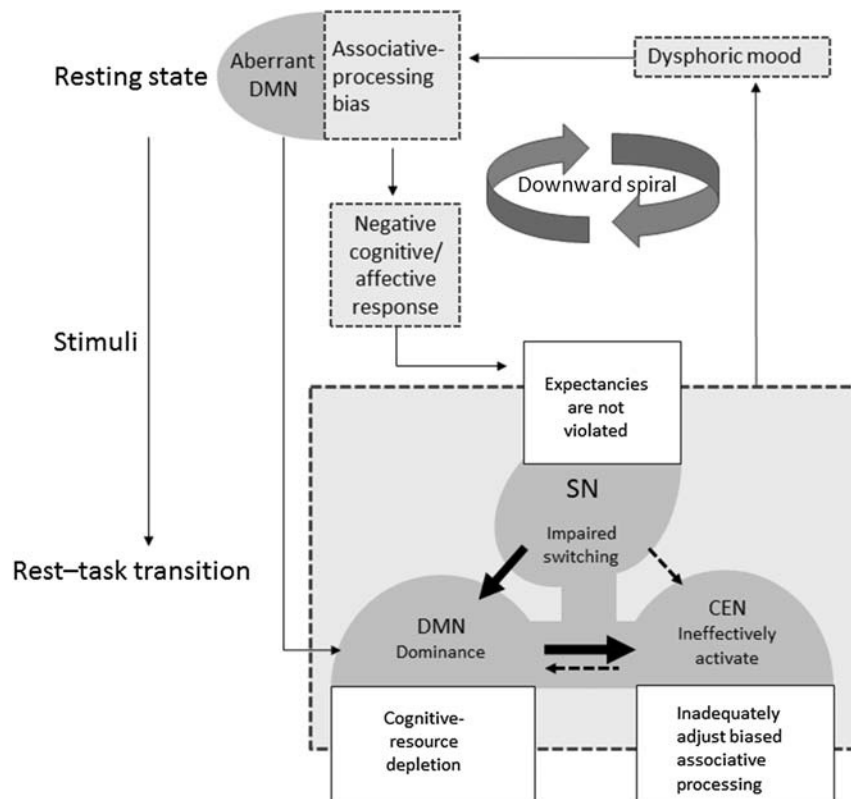
among adolescents 13 to 18 years old.<sup>2,3</sup> MDD is characterized not only by persistent negative mood and lack of motivation, but also by maladaptive thinking styles and specific impairments in integrating information. These cognitive disturbances present not only in people suffering from depressive disorders but also in people with elevated negative mood. Over the years, researchers have explored risk factors for, and potential treatment approaches to, MDD from both biological and psychological perspectives.

Cognitive factors, which have been highlighted in all psychological models, suggest that the interaction of stress and premorbid vulnerabilities contributes to depressive episodes throughout the life span.<sup>4</sup> Recently, researchers suggested that cognitive vulnerability may represent an endophenotype for depression.<sup>5</sup> Cognitive-vulnerability models themselves include a broad array of risk factors, as in Beck's cognitive model (e.g., information-processing biases, negative self-schemas),<sup>6</sup> hopelessness theory (e.g., depressogenic attribution styles to event causes, consequences, and the self),<sup>7</sup> and response-styles theory (e.g., rumination).<sup>8</sup> Given this array of vulnerability factors, researchers have sought to explore a new model that integrates the core factors of prominent theories in order to provide a more holistic understanding of cognitive vulnerability.

The dual-process theory of cognitive vulnerability, which has been supported by many behavior experiments,<sup>9–12</sup> integrates the main vulnerability factors into one model from an information-processing perspective.<sup>13</sup> According to this model, two information-processing modes correlate with the cognitive vulnerability to depression: one is called *associative/implicit mode*, which is characterized by quick, effortless processing based on well-learned associations, and the other is called *reflective/explicit mode*, which is characterized by slow, effortful processing that requires more intention and awareness.<sup>9,14</sup> Dual-process theory emphasizes negatively biased, self-referential, associative processing as the foundation for cognitive vulnerability, which may be overcome by corrective reflective processing. Additionally, the theory raises three scenarios of interplay between associative and reflective processing that may lead to a downward spiral and then into more severe forms of dysphoria (see Figure 1). The dual-process theory thus provides a relatively parsimonious framework of cognitive vulnerability. It emphasizes the dynamic imbalance between two cognitive processes in the generation and persistence of negative mood. In addition, the model integrates

the core factors of prominent cognitive-vulnerability theories, such as the negative information-processing biases and negative self-schemas of Beck's cognitive model, the depressogenic attribution in hopelessness theory, and the rumination in response-styles theory.<sup>14</sup> There remains a gap, however, between the symptom/behavior level of psychopathological theory and the associated biological underpinnings of depressive vulnerability.

Advances in brain imaging, especially in the field of intrinsic neural network research, may provide a useful tool to identify the missing neural-behavioral links (see Text Box 1). Over the past two decades, neuroimaging research using affective or cognitive tasks to study depressive vulnerability has shown that altered corticolimbic connectivity contributes to the generation of excessive and persistent negative affect.<sup>15,16</sup> Additionally, given that substantial evidence has demonstrated the functional importance of spontaneous BOLD activity on task-related responses and has highlighted its predictive nature for subsequent behavioral and mental states,<sup>17–20</sup> resting-state functional magnetic resonance imaging (fMRI) has been increasingly utilized to probe cognitive-vulnerability factors



**Figure 1.** Aberrant intrinsic network interaction model that integrates the dual-process model of cognitive vulnerability, which has been adapted from Beavers (2005).<sup>14</sup> The dual-process model includes two modes of information processing: (1) an associative mode involving quick, effortless processing, and (2) a reflective mode involving slow, effortful processing. We propose that abnormally increased resting-state DMN activity and connectivity, along with the corresponding biased associative processing (depressive rumination), contribute to the foundation of cognitive vulnerability. In the period of rest-to-task transition, aberrant network interactions contribute to three scenarios in which an associative bias cannot be corrected, thus promoting cognitive vulnerability. These three scenarios are (1) DMN dominance over the CEN (cognitive-resource depletion), (2) abnormal SN switching between the DMN and CEN (associative bias does not violate internal expectancies and trigger reflective processing), and (3) failure to activate the CEN effectively (reflective processing being triggered but failing to accurately adjust associative bias). As a result, a feedback loop between negative bias and dysphoria occurs, leading to a downward spiral. The solid lines in the triple-network model indicate enhanced interactions, while the dotted lines indicate attenuated interactions. CEN, central executive network; DMN, default mode network; SN, salience network.

### Text Box 1 Glossary

#### Functional magnetic resonance imaging (fMRI)

A form of noninvasive neuroimaging based on blood-oxygen-level-dependent (BOLD) signals in the brain in vivo.

#### Blood-oxygen-level-dependent (BOLD) signal

The measurement of metabolic activity in the brain based on the magnetic resonance imaging contrast of blood deoxyhemoglobin levels arising from changes in local blood flow.

#### Brain network

*Network* originally referred to a physical system that can be represented by a graph consisting of nodes and edges. In the field of neuroscience, brain networks can be defined by structural connectivity or functional interdependence. The former is based on the anatomical linkage of its neurons, whereas the latter refers to joint activity in different brain structures that is codependent under variation of a functional or behavioral parameter.

#### Independent component analysis

A computational technique that separates a multivariate signal into additive components based on the assumption that the components arise from statistically independent non-Gaussian sources.

#### Network node

*Node* refers the component of network linked by edges. In the field of neuroscience, the nodes in structural networks are typically considered to be brain areas defined by cytoarchitectonics, local circuit connectivity, output projection target commonality, and input projection source commonality. The functional nodes are commonly identified by inferences concerning the effects of brain lesions on cognitive function (historically) or by relating the joint activation or deactivation of brain areas to different cognitive functions.

#### Functional connectivity

The statistical interrelation of variables representing temporal changes in different network nodes. In other words, functional connectivity refers the temporal correlation of a neurophysiological index measured in different brain areas, with the consequence that coactivating brain regions are usually identified as functional brain networks.

#### Large-scale network

These networks are neural systems that are distributed across the entire extent of the brain. Based on the technological and methodological advances of structural and functional brain connectivity, large-scale network studies focus on revealing how cognitive functions arise from interactions within and between distributed brain systems.

#### Intrinsic network

Intrinsic networks are also called *intrinsic connectivity networks*. Originally, the intrinsic network referred to a large-scale network of interdependent brain areas observed at rest, which typically were identified by independent component analysis on BOLD spontaneous fluctuations. Recently, emerging evidence shows that the intrinsic network architecture also is present across a wide variety of task states, suggesting that this form of interconnectedness is an “intrinsic” standard architecture of functional brain organization.

implicated in depression.<sup>21</sup> Specifically, aberrant resting-state activity and functional connectivity in cortical midline structures have been reliably observed in at-risk,<sup>22,23</sup> depressed,<sup>24,25</sup> and formerly depressed populations.<sup>26,27</sup> Moreover, abnormality in the default-mode network (DMN), a principal intrinsic brain network including cortical midline structures, is increasingly associated with cognitive vulnerability among at-risk and depressed individuals.<sup>28,29</sup> Other large-scale neural networks, such as the central executive network (CEN) and salience network (SN), also seem to play a role in biased attention and processing of affective information in depression.<sup>30–32</sup> Thus, understanding how there might be simultaneous dysfunction in multiple networks (see Text Box 2) may elucidate the neural nature of cognitive vulnerability.<sup>37,48,49</sup>

According to studies in healthy individuals, the CEN typically shows increased activation during external stimulus-driven cognitive and affective information processing, whereas the DMN shows decreased activation with tasks in which self-referential processing is not required.<sup>35,38</sup> In addition,

emerging evidence shows that the SN, especially the right fronto-insular cortex, is responsible for switching DMN-CEN interactions.<sup>40,41,50,51</sup> Briefly, during the externally oriented processing there is typically anti-correlated relationship between the DMN and CEN, which is regulated by the SN (see Figure 2).<sup>43–45</sup> Since vulnerability-stress models of depression emphasize an interaction of cognitive diatheses with negative life events leading to the development and onset of depressive episodes,<sup>4</sup> investigating abnormal brain responses to emotional or cognitive stimuli in the rest-task transition period (from an internally oriented processing state to an externally oriented stimulus/task-induced processing state) are especially important to understanding the emergence of cognitive vulnerability and depression. In our section below on rest-task transition, we focus on the role of DMN suppression in support of externally oriented cognition to negative life events and on the dynamic interaction among three intrinsic networks. Previous studies demonstrated that patients with MDD, at-risk individuals, and remitted depression subjects

### Text Box 2 Intrinsic Network Research and the Triple-Network Model

The intrinsic network research originally emerged from the resting-state brain activity or connectivity studies. After Raichle and Greicius<sup>33,34</sup> identified “default mode” network, which exhibits high levels of activity at rest and becomes deactivated with tasks needing specific goal-directed behavior, Fox and colleagues<sup>35</sup> formulated a model in 2005 that included two tightly locked, but anti-correlated, networks—namely, the task-negative network and task-positive network. In 2007, Seeley and colleagues<sup>36</sup> demonstrated that the task-positive network actually comprises two dissociable networks: an executive network and a salience network (SN). Based on the previous studies, Menon and colleagues<sup>37</sup> proposed a triple-network model comprising the default mode network (DMN), SN, and central executive network (CEN) as the core neurocognitive networks, especially for investigating psychopathology in psychiatric and neurological disorders. The triple-network model is now one of the most widely utilized models for understanding the neural bases of neuropsychiatric disorders. It is therefore the one that we have used in this review.

The DMN comprises mainly the medial prefrontal cortex and adjoining ventral anterior cingulate cortex, posterior cingulate cortex, bilateral inferior parietal cortex, and medial temporal lobe.<sup>33</sup> The DMN is involved in self-referential/ internally directed information processing and is typically deactivated during external stimulus-driven cognitive processing.<sup>38</sup>

The CEN comprises mainly the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex, and is responsible for high-level cognitive functions. The CEN is involved in control processes during goal-directed/externally oriented tasks and in regulating emotional responses, particularly those mediated via the DLPFC.<sup>36,39</sup>

The SN is anchored in the anterior insular cortex and dorsal anterior cingulate cortex, and also includes two key subcortical structures: the amygdala and substantia nigra/ventral tegmental area, which are important for detecting emotional and reward saliency.<sup>40</sup> The SN is involved in detecting and orienting to both external and internal salient stimuli and events.<sup>36</sup> The anterior insular cortex is critically involved in maintaining and updating representations of current and predictive salience, and contributes to appropriate behavioral responses to salient stimuli by switching between DMN-related self-referential, and CEN-related goal-directed, cognitive activity.<sup>41,42</sup>

Although originally identified from resting-state fMRI data, the CEN, DMN, and SN can also be readily identified across a wide range of cognitive tasks. The responses of those networks increase and decrease proportionately, and often antagonistically, with the demands of general external cognitive tasks. For instance, the CEN and SN typically show increased activation during external stimulus-driven cognitive and affective information processing, whereas the DMN shows decreased activation with tasks in which self-referential processing is not required.<sup>33,34</sup> However, the DMN and CEN can also positively couple when organizing internal self-relevant thought (e.g., autobiographical planning).<sup>43–45</sup> Dynamic engagement and disengagement of those core neurocognitive networks are prominent in many cognitive tasks.<sup>41,46,47</sup>

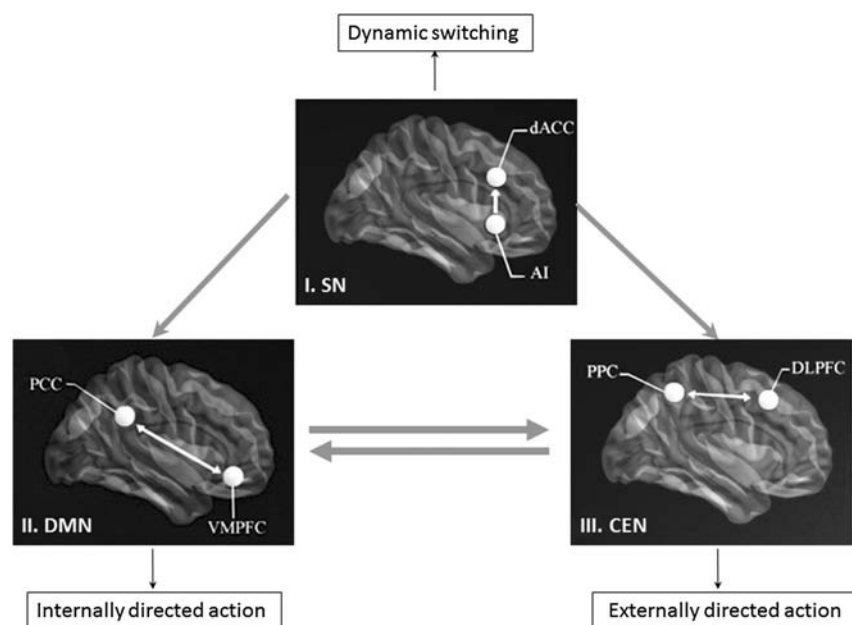
consistently show the abnormal connectivity and interaction between the DMN and CEN, as well as dysregulation of the SN, when processing external cognitive or affective stimuli.<sup>27,55,56</sup> Therefore, the resting state-related prominent abnormality of the DMN, along with an imbalance among intrinsic networks in the rest-task transition period, has been proposed as the specific neural susceptibility feature of depression.

The aim of this review is to synthesize current neuroimaging research to reinterpret the formation of cognitive vulnerability and subsequent depression from the perspective of intrinsic organization and cross-network interaction. Based on the dual-process model, we will describe how abnormal activities and interactions among the DMN, CEN, and SN can provide insights into the emergence of cognitive vulnerability and MDD. Specifically, as first proposed by Sheline and colleagues<sup>57,58</sup> and subsequently discussed in multiple studies,<sup>24,28,59–61</sup> the hyperactivity in the DMN leads to a negative associative-processing bias commonly associated with negative self-referential processes, which forms the neural foundation of cognitive vulnerability to depression. In addition, abnormal cross-network interactions during rest-task transitions, which include three scenarios, lead to the failure to correct negative associative-processing bias, thereby facilitating and stabilizing the cognitive vulnerability (see Figure 2). We will describe these mechanisms in detail in the next sections. Though

research on functional connectivity and intrinsic networks does not provide a direct proxy for anatomic/structural connectivity, the integrative framework presented here extends beyond the phenomenological dimensions of depression and local functional impairments. It suggests new research directions addressing both behavioral and neuronal features in cognitive vulnerability, and potentially informs the development of targeted interventions for MDD.

### ABERRANT RESTING-STATE DMN AND ASSOCIATIVE-PROCESSING BIAS

The dual-process model suggests that negatively biased self-referential associative processing is the foundation for cognitive vulnerability to depression.<sup>14</sup> Though many vulnerability factors are associated with biased self-referent information, maladaptive rumination plays a primary role in mediating the internalization of negative self-representations and onset of depression symptoms.<sup>62</sup> Research suggests that maladaptive rumination is characterized by spontaneous, narrowly focused, self-referential associative processing.<sup>63</sup> In addition, there is a strong overlap between the DMN and the cortical network that mediates associative processing on the medial prefrontal cortex (medial PFC), medial temporal lobe, and medial-parietal cortex.<sup>64</sup> Recently, increasing evidence suggests that maladaptive rumination-related resting-state



**Figure 2.** Schematic figure of triple-network model showing the SN-induced coordination between the DMN and CEN. According to this model, the SN (I) mediates the “switching” between the DMN (II) and CEN (III) to guide appropriate responses to salient stimuli.<sup>40</sup> Saliency signals are integrated in the anterior insular cortex of the SN, and then causally influence signals in the DMN and CEN, which support internally directed and externally directed cognition, respectively.<sup>41,47</sup> In light of recent work that suggests the existence of distinct functional subdivisions within the insular cortex,<sup>52,53</sup> the right anterior insular cortex is now thought to be the specific brain region that assists in switching between networks. The large dots show the key nodes of each network in the triple-network model. AI, anterior insular cortex; CEN, central executive network; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; SN, salience network; PPC, posterior parietal cortex. Adapted from Uddin (2014)<sup>51</sup> and Uddin & Menon (2009).<sup>54</sup>

DMN activity is associated with the generation of cognitive vulnerability.<sup>60</sup> Specifically, Bar<sup>63</sup> states that the neural basis of rumination is resting medial PFC hyperactivity coupled with increased functional connectivity between the medial PFC and anterior cingulate cortex (ACC). This increased functional connectivity, in turn, suppresses medial temporal lobe activity and constrains normally broad associative processing and the generation of a positive mood, leading to ruminative processes and negative mood states.

Neuroimaging studies have supported Bar’s hypothesis that persistent hyperactivity in the medial PFC and its neighboring ventral ACC regions, as well as their relationship with the medial temporal lobe, plays a core role in the cognitive vulnerability to depression. Berman and colleagues<sup>28</sup> examined the relationship between DMN functional connectivity and rumination, both at rest and in a short-term memory task. During the rest period, MDD participants exhibited increased DMN connectivity in the subgenual ACC, which correlated with self-report rumination and hyperconnectivity between the medial PFC and medial temporal lobe. Similarly, a study on first-episode, unmedicated MDD subjects found significantly greater functional connectivity between the rostral ACC and parahippocampal gyrus at rest.<sup>65</sup> Recently, Sambataro and colleagues<sup>66</sup> investigated the function of multiple DMN subsystems at rest in MDD and showed increased connectivity, increased low-frequency band spectral power in the medial PFC, subgenual ACC, and rostral ACC, and aberrant interactions between the rostral ACC and hippocampus. Moreover,

using an unsupervised machine-learning approach with a network derived from resting-state fMRI data, including the subgenual ACC, medial PFC, and superior temporal gyri, Zeng and colleagues<sup>67</sup> demonstrated a highly discriminative power for accurate identification of MDD. Schilbach’s study using a meta-analytically informed network analysis<sup>68</sup> also showed the subgenual ACC to be a hub of resting-state hyperconnectivity in the introspective socio-affective network in depressive individuals. Thus, converging evidence from a number of brain-imaging studies suggests that the generation of maladaptive rumination is associated with resting hyperactivity in the medial PFC and with hyperconnectivity between the medial PFC and both the ventral ACC and medial temporal lobe.

Bar’s hypothesis has been further supported by consistent evidence of enhanced functional connectivity among anterior DMN regions in MDD patients. Using independent component analysis, Greicius and colleagues<sup>69</sup> first explored DMN abnormalities in major depression and suggested that the DMN functional connectivity in depression, which was associated with the ruminative nature of depressive subjects, was disproportionately driven by increased activity in the subgenual ACC. Importantly, numerous other studies have replicated the basic findings of that study.<sup>57,70,71</sup> In addition, using multivariate Granger causality analysis of resting-state data, Hamilton and colleagues<sup>72</sup> found that medial PFC and subgenual ACC activities were mutually reinforcing in MDD and that the medial PFC-to-subgenual ACC connectivity correlated with levels of depressive rumination. In 2012, we

provided the first direct evidence of increased resting-state functional connectivity in the anterior medial cortex regions (especially the medial PFC and rostral ACC) that correlated with rumination scores from first-episode, treatment-naïve MDD patients.<sup>24</sup> That finding has been supported by studies in adolescents experiencing first-episode MDD.<sup>25</sup> Using a unique four-year follow-up sample of children with a history of preschool-onset MDD, Gaffrey and colleagues<sup>73</sup> also demonstrated abnormal subgenual ACC functional connectivity and found correlations between dysregulated emotional behavior and subgenual ACC/medial PFC connectivity. The subgenual ACC and rostral ACC formed the affective division of ACC, which is activated by tasks with affective or emotional content and also deactivated by cognitively demanding tasks.<sup>74</sup> Hence, the joint hyperactivity in those DMN nodes, by leading to ruminative processes, may have a critical role in the formation of cognitive vulnerability.

Neuroimaging evidence from subjects at risk for MDD and from nonclinical populations provides additional evidence that the DMN is involved in ruminative processes and contributes to cognitive vulnerability. Norbury and colleagues<sup>22</sup> examined resting-state fMRI data from 15 healthy at-risk participants having a biological parent with MDD and from 15 healthy controls. Relative to the controls, the subjects with positive family history showed significantly greater DMN connectivity in the left dorsomedial PFC, left medial temporal lobe, orbitofrontal cortex, and left precuneus. The researchers suggest that this pattern may represent a ruminative vulnerability. Similarly, Kross<sup>75</sup> reported that rumination induction in healthy subjects activated a network that included the subgenual ACC and medial PFC, and that this network activity was greater during induced rumination than during “analyze” or “accept” conditions. Moreover, activity in this network correlated positively with increases in negative affect during induced rumination. Recently, Liu<sup>76</sup> and Fielder<sup>23</sup> provided new evidence independently for the altered resting-state anterior DMN connectivity in healthy siblings of MDD patients<sup>76</sup> and in women with subclinical depression but without a history of MDD.<sup>23</sup>

In summary, emerging evidence strongly indicates that elevated resting-state activity in anterior DMN regions and the greater functional connectivity among them are associated with rumination: a narrow associative-thinking pattern and cognitive vulnerability factor in depression. However, two points are worth mentioning. First, we propose that abnormal anterior DMN activity at rest may reflect only brooding, a subcomponent of rumination that involves negative self-focus and is hypothesized to be more strongly associated with depressive symptoms both in concurrent and longitudinal analyses.<sup>77</sup> The other subcomponent of rumination—namely, reflection—more likely relates to reflective processing in the dual-process model, which is a purposeful turning inward to alleviate one’s depressive symptoms.<sup>14,78,79</sup> Indeed, Hamilton and colleagues<sup>72</sup> reported that greater DMN activity in MDD patients at rest was associated with higher levels of brooding

and lower levels of reflection. Berman and colleagues<sup>28</sup> reported a similar result. Second, there are some discrepant studies in the literature, which might be due to the differences in sample characteristics or analysis methods, such as using the a priori defined region-of-interest correlation approach versus whole-brain analyses,<sup>79,80</sup> using independent component analysis at the group level versus on individual data sets,<sup>81</sup> or applying a newly developed method.<sup>82</sup> Deployment of more uniform methodologies may help resolve these discrepancies.

## ABERRANT NETWORK INTERACTIONS DURING REST-TASK TRANSITIONS: THREE SCENARIOS

### DMN Dominance: Cognitive-Resource Depletion

Although persistent resting-state DMN hyperactivity and heightened spontaneous rumination are core features of cognitive vulnerability, DMN hyperactivity may also occur in nondepressed individuals. In nondepressed individuals, however, that state is typically transient, and they are able to shift quickly toward task-based deactivation to support stimulus-driven, goal-directed cognitive processes. In other words, the resting-state “imbalance” within intrinsic networks may stop, and the development of cognitive vulnerability and dysphoric mood may be suspended.<sup>83</sup> However, patients with MDD consistently show both a lack of DMN suppression and impaired performance during task-induced states, indicating that the DMN dominance continues and that its residual activity interferes with subsequent attentional and cognitive processing. Johnson’s study<sup>84</sup> provided direct evidence that patients with MDD show less DMN deactivation during externally oriented cognitive processing—an effect that was positively correlated with rumination. Hence, the authors suggested that depression pathology may involve a difficulty with disengaging from self-reflection. Grimm and colleagues<sup>85</sup> investigated negative BOLD responses in DMN regions during the presentation of emotional pictures and reported reduced rest-to-task attenuation of DMN activity in MDD patients. Importantly, that reduced attenuation was associated with strong feelings of hopelessness. Furthermore, Mitterschiffthaler and colleagues<sup>86</sup> reported significant engagement of the rostral ACC and right precuneus in MDD subjects during an emotional Stroop task. The rostral ACC activation in MDD subjects was positively correlated with impaired performance on trials with negative words. A hyperactive DMN has also been shown to result in impaired cognitive performance in working-memory tasks, passive viewing, and implicit-recognition tasks for negative images.<sup>56,87,88</sup>

Based on the above neuroimaging studies, both the elevated DMN activity during resting state and the increased DMN activity (less suppression) during task-induced states play an important role in the pathophysiology of MDD. The latter is central to the first dual-processing scenario for developing cognitive vulnerability (Figure 1): reflective processing may not override the negatively biased associative processing when some cognitive load disrupts, which then

leads to cognitive vulnerability. This finding was confirmed by Wenzlaff and colleagues<sup>89</sup> using a series of behavior tasks in remitted and currently depressed individuals. Specifically, although remitted patients did not have a negative bias at baseline, biased performance under a cognitive-load condition was predictive of future depressive symptoms. In addition, behavioral,<sup>90</sup> pupillary,<sup>91</sup> and electrophysiological<sup>92</sup> data support the notion that depressed individuals engage in increased intrinsic processing (e.g., focusing on negative automatic thoughts or rumination), which potentially taxes resources that would otherwise be allocated to cognitive tasks. Recently, Nixon and colleagues<sup>93</sup> reported the first direct evidence of persistent excessive DMN activity during tasks in remitted MDD patients, which suggests that task-based DMN hyperconnectivity may result in cognitive and attentional bias and increase the risk of depression. Therefore, DMN dominance may be the neural basis for the role of cognitive-resource depletion in the development of vulnerability and then depression.

Recent work on DMN-CEN anti-correlation provides potential evidence for this mechanism. The optimal attunement between the DMN and CEN is thought to reflect efficient intrinsic brain organization.<sup>35,94</sup> During the processing of externally directed stimuli, the deactivation of the DMN and the increased activation in the CEN occur concurrently and timely for ensuring appropriate and successful responses.<sup>36,46</sup> In the rest-task transition period, however, both depressive and at-risk individuals show abnormal DMN dominance, which induces decreased DMN-CEN anti-correlation and subsequently depletes cognitive resources.<sup>95</sup> This phenomenon may arise in two ways. In the first, exaggerated spontaneous DMN activity may persist following the rest-task transition, reduce recruitment of cognitive-control resources, and prevent distraction from rumination.<sup>25,96</sup> This DMN persistence is evidenced by the rumination-related lack of DMN suppression in a non-self-referential task.<sup>84</sup> Similarly, using a new quantitative method to compute the extent to which DMN activity levels exceed task-related network activity over the course of the resting-state scan, Hamilton and colleagues<sup>72</sup> showed that increasing levels of DMN dominance were associated with higher levels of brooding and lower levels of reflection in MDD. In addition, Davey and colleagues<sup>97</sup> reported that the subgenual ACC–ventromedial PFC connectivity in MDD increased in resting state and that this change in functional connectivity could predict the relative activity of CEN regions, thus suggesting that dysfunctional connectivity with the subgenual ACC may influence executive/attentional processes. Thus, the attenuated DMN-CEN anti-correlation stemming from abnormal DMN dominance in the rest-task transition may induce cognitive-resource depletion leading to cognitive vulnerability to depression.

The second way in which abnormal DMN dominance in MDD may arise is from automatic, effortless, negatively biased information processing at a preconscious level, which activates the DMN and attenuates the influence of otherwise distracting cognitive processing. Many studies related to negative stimulus

processing mentioned above support this mode of developing DMN dominance.<sup>56,86,98</sup> Such studies consistently reported heightened responses in the amygdala, along with higher activity in the DMN and lower activity in the CEN. Moreover, spontaneous activity in the amygdala has been shown to positively predict the activity of the medial PFC and to negatively predict the activity of the middle frontal gyrus.<sup>99</sup> A longitudinal study further showed that amygdala-ventromedial PFC connectivity was predicted by early-life stress and associated positively with depressive symptoms in female adolescents.<sup>100</sup> A recent study further reported increased, sustained amygdala reactivity involving the involuntary processing of salient negative information associated with all the dimensions of trait rumination.<sup>101</sup> Thus, aberrant DMN dominance during prior processing of negative emotional stimuli in MDD may be caused by excessive input from the SN nodes, and be associated with aberrant attention allocation and switching. We will interpret the related mechanisms in the next section.

In summary, the DMN-dominant state during rest-task transition may arise from the persistence of resting DMN activity or from quick activation of the DMN during negative stimulus processing. This persistence depletes cognitive resources and leads to a sustained negative cognitive bias, which then facilitates the development of cognitive vulnerability to depression.

### **Impaired SN Switching Between DMN and CEN: Expectancies Are Not Violated**

In Menon's triple-network model,<sup>37</sup> the SN—which is anchored in the dorsal anterior cingulate cortex, fronto-insular cortex, amygdala, and ventral striatum—is involved in bottom-up detection of salient events and in switching between other large-scale networks to facilitate appropriate allocation of attentional and cognitive/executive resources when a salient event is detected. Using the Granger causality analysis method in both of resting-state and task-state data, Sridharan and colleagues<sup>41</sup> discovered that the right fronto-insular cortex–ACC network, especially the right fronto-insular cortex, plays a causal role in DMN-CEN switching. Recently, and using a novel technique for analyzing resting-state data, Goulden and colleagues<sup>50</sup> independently validated the role of SN in driving the switching between the DMN and CEN. Another study involving a combination of fMRI and diffusion tensor imaging data also supported the critical role of the right fronto-insular cortex in switching between brain networks for complex, flexible cognitive processing.<sup>47</sup> Furthermore, by combining transcranial magnetic stimulation (TMS) and fMRI, Chen and colleagues<sup>102</sup> successfully demonstrated that single-pulse TMS of an SN site enhanced both within-SN and within-CEN connectivity, whereas TMS stimulation of a CEN site enhanced only within-CEN psychophysiological connectivity. In summary, the SN switching role between the DMN and CEN (see Figure 2) has been strongly supported by converging evidence in healthy subjects and highlights the possibility that the atypical engagement of the SN is a feature of neuropsychiatric disorders.<sup>51</sup>



A growing body of evidence demonstrates that the SN's switching function is impaired in MDD and at-risk individuals.<sup>103,104</sup> For instance, medication-naïve adolescents with MDD showed reduced activation in the fronto-insular cortex and dorsolateral PFC during an attention-switching task.<sup>105</sup> Strigo and colleagues<sup>106</sup> further demonstrated that in MDD, altered right fronto-insular cortex function, along with increased activity in the ventromedial PFC and rostral ACC and decreased activity in the dorsolateral PFC, is associated with an impaired ability to effectively prepare for environmental changes. Similarly, Hamilton and colleagues<sup>72</sup> examined the right fronto-insular cortex response during initiation of ascents in DMN and CEN activity and showed that right fronto-insular cortex plays a differential role in DMN/CEN dominance switching in MDD subjects versus controls. This model is further supported by Manoliu and colleagues' recent study.<sup>107</sup> In addition, through comparing task-based brain function of individuals with high or low risk of developing MDD, Peterson and colleagues<sup>104</sup> described a neural system, including insular and other nodes in cortical attention circuits, as the risk endophenotype for MDD. Recently, Kaiser and colleagues<sup>56</sup> compared the neural activation during emotion-word and color-word Stroop tasks in participants with subclinical depression. They suggested that affective interference stems from the increased salience of negative emotional information, coupled with the difficulty in shifting resources toward the external environment. That study further supported the SN's abnormal function in switching between the DMN and CEN in vulnerable individuals.

Besides the direct measurement of activity or functional connectivity of the SN nodes in MDD and vulnerable individuals, many studies have showed that the abnormal switching function of the SN is associated with mood-congruent, negative-response biases, a well-known vulnerability factor emphasized in Beck's cognitive model of depression.<sup>108</sup> Specifically, the amygdala contributes to the biased processing of both explicitly and implicitly negative emotional stimuli in at-risk depressive individuals,<sup>31,109,110</sup> MDD,<sup>111–114</sup> and remitted MDD patients.<sup>115</sup> The anterior insula and dorsal ACC also participate in the formation of these biases.<sup>116,117</sup> A recent fMRI study showed that MDD patients develop a pessimistic attitude toward the emotional meaning of external events—an attitude associated with abnormal activation in the medial PFC, dorsolateral PFC, and insular cortex.<sup>118</sup> Therefore, the misinterpretation of external cues by the insula due to unpleasant previous experiences may be a central underlying mechanism of depression-related dysregulation. Similarly, in a voxel-wise, whole-brain meta-analysis, Hamilton and colleagues<sup>119</sup> showed that MDD patients had elevated activity in the amygdala, insula, and dorsal ACC, but decreased activity in the dorsolateral PFC, during the process of negative emotional stimuli. The authors suggested that in depression, negative information could induce a heightened neural response in the SN but fail to be propagated to the CEN for contextual processing and reappraisal. Indeed, in 2008, a

pathway-mapping analysis provided direct fMRI evidence for that hypothesis: regulation of emotion through the amygdala to the ventrolateral PFC could predict reappraisal failure and more sustained negative emotion.<sup>120</sup> To sum up, several core regions in the SN are critically involved in the formation of mood-congruent negative-response biases and subsequently in the change of CEN activity associated with cognitive control.

The aforementioned SN-related, mood-congruent, negative-bias processing could play a role in the second scenario of failing to correct biased associative processing in the dual-process model (see Figure 1): when the results of associative processing are congruent with one's negative internal expectancy (e.g., negative self-referential schemas or representations related to one's self-worth), expectancies will not be violated. By contrast, when healthy individuals with optimism biases confront negative external stimuli, cognitive conflict would be recognized automatically, and attention would then be disengaged from the negative thoughts. Previous studies showed that conflict signaling was reduced in individuals with negative thoughts/mood due to their mood-congruent attention and memory biases.<sup>121</sup> Accordingly, in individuals at risk for depression, attentional resources could not reallocate appropriately to disengage from the situation; instead, the resources continue to focus on self-referring negative information.<sup>122</sup> Along the same lines, observations in healthy individuals with high brooding scores show that more attentional control is needed to successfully disengage from negative information.<sup>123</sup> Therefore, the “impaired disengagement” of attention based on the mood-congruent negative bias in MDD would facilitate not only sustained maladaptive rumination but also impaired cognitive performance. In summary, we propose that in the context of mood-congruent, negative-bias processing, impaired SN switching between the DMN and CEN underlies, at least in part, the cognitive vulnerability to depression.

### **Failure to Effectively Activate CEN: Reflective Processing Does Not Adequately Adjust Biased Associative Processing**

In the third scenario of the dual-process model, which may involve a failure of CEN activation (see Figure 1), it is posited that cognitive vulnerability to depression is facilitated when reflective processing does not adequately adjust output from associative processing. In other words, when an individual tries to regulate emotion voluntarily (i.e., to reappraise) through reflective processing but fails, an associative bias is maintained or even amplified. Two cognitive-vulnerability factors are likely involved in reflective processes related to emotion regulation: reflective rumination<sup>74</sup> and depressogenic attributional styles<sup>7</sup> (i.e., regarding the self and the causes and consequences of negative events) based on hopelessness theory. When vulnerable individuals confront negative events, both of those factors will guide them to spontaneously use emotion-regulation strategies that could be directed against the increased negative emotion stemming from elaboration on the meaning of unpleasant events. However, failure to regulate

will lead the individual to fall into more negative cognition, depressive rumination, and dysphoria.

Emotion-regulation deficits are a central characteristic of depressed individuals. Though previous studies showed that different types of emotion-regulation strategies (e.g., automatic vs. voluntary, distraction vs. reappraisal) are associated with different neural mechanisms, both strategies are subserved by common top-down control areas in the CEN (especially the dorsolateral PFC node) to effectively allocate attention to the external stimuli.<sup>124,125</sup> Furthermore, numerous studies suggest that aberrant voluntary emotion-regulation in MDD is related to hypoactivity in CEN nodes.<sup>126,127</sup> However, recent evidence has also pointed to hyperactivity in DMN components. Smoski and colleagues<sup>128</sup> found that remitted MDD showed significantly greater rostral ACC activation and simultaneously decreased midfrontal gyrus activation during the reappraisal of sad images (in contrast to attending to sad images). Similarly, Sheline and colleagues<sup>58</sup> reported that when subjects with MDD reappraised negative pictures actively, widely distributed elements of their DMNs failed to deactivate. Erk<sup>129</sup> and Johnstone<sup>130</sup> also found that MDD patients show significantly diminished responses in the dorsolateral PFC, but increased activation in DMN nodes, when performing an effortful reappraisal task for negative emotion. In a small study including only 12 MDD patients, Dillon and colleagues<sup>131</sup> reported recently that dorsolateral PFC activity correlated inversely with depressive severity, though no group differences in reappraising negative pictures were found. Another follow-up study of remitted MDD participants employing sad mood provocation has added new evidence showing that expansive medial PFC reactivity can predict subsequent depressive relapse over an 18-month follow-up period.<sup>16</sup> The authors linked medial PFC reactivity in remitted MDD participants to inefficient recruitment of the PFC in attempts to cognitively regulate negative emotion. Recently, two studies in remitted MDD reported similarly reduced PFC reactivity during negative feedback, which was associated with the rumination and possibly impaired the adaptive reappraisal of negative experience.<sup>132,133</sup> Thus, emerging evidence suggests that during the cognitive regulation of negative events, the failure to regulate and the generation of cognitive vulnerability are not only associated with the decreased activation in CEN nodes but also with increased activation in DMN nodes.

Since CEN hypoactivity and DMN hyperactivity could be occurring simultaneously during impaired cognitive regulation in MDD, it raised a question whether attenuated CEN modulation is a primary effect of CEN hypoactivity or a secondary effect of interference from DMN activity. In a recent study combining TMS with fMRI, Chen and colleagues<sup>102</sup> reported direct evidence of a causal regulatory relationship primarily from the CEN to the DMN. Specifically, single-pulse excitatory stimulation of a CEN node (posterior middle frontal gyrus) induced negative DMN connectivity with the CEN, whereas inhibitory repetitive TMS to the same stimulation site induced the disinhibition of DMN activity on the medial PFC.

Two other TMS studies presented further evidence that repetitive TMS on the dorsolateral PFC could modulate interactions between the DMN and CEN by normalizing depression-related DMN hyperconnectivity.<sup>134,135</sup> As more anti-correlation between the two networks was induced, the clinical efficacy of the TMS increased. Interestingly, in a recent double-blind, six-month trial examining changes in the neural circuitry involved in emotion regulation after antidepressant treatment, only changes in CEN nodes (dorsolateral PFC and Brodmann area 10) that were engaged while subjects performed a negative affect-regulating task correlated with changes in depression severity over the following six months.<sup>136</sup>

In summary, previous studies suggest that failure to effectively activate the CEN and the corresponding reduced effect on the DMN mainly contribute to the unsuccessful voluntary regulation of negative emotion, thus allowing negative cognitive/affective responses to persist and facilitating the development of depressive vulnerability.

## CONCLUSIONS AND FUTURE DIRECTIONS

In this review, we used a dual-process framework and built upon the literature of intrinsic networks to integrate well-established MDD cognitive-vulnerability factors and corresponding neural mechanisms. We propose that abnormally increased resting-state DMN activity and connectivity (mainly in anterior DMN regions) and corresponding depressive rumination contribute to the development of cognitive vulnerability. Furthermore, in the period of rest-to-task transition, three kinds of aberrant network interactions may facilitate the occurrence of cognitive vulnerability. Specifically, when confronting negative life events or stimuli, DMN dominance (persisting due to increased resting activity and facilitated by automatic, biased information processing), abnormal SN-mediated switching between the DMN and CEN (related to a negative schema and mood-congruent negative bias), and failure to effectively activate the CEN (related to reflective rumination, negative attribution style, and corresponding emotion-regulation impairment). A focus on interrelated networks and brain activity changes between rest-task transitions provides an approach for future research into inter-individual differences in vulnerability and resilience. Several outstanding questions remain, however, and need to be explored in depth.

First, although an increasing number of neuroimaging studies have investigated cognitive vulnerability to depression, more systematic research is required to test and confirm the validity of our framework. For instance, longitudinal fMRI studies with comprehensive assessment of cognitive-vulnerability factors would allow us to investigate the intrinsic network changes in predicting future occurrences of depression. To date, only a few studies have compared brain system activity among never-depressed individuals with vulnerability factors, currently depressed individuals, and remitted depressed individuals. A more systematic research approach, including both cross-sectional and longitudinal studies, is needed to develop the models for mapping the neural patterns.

Second, the neurobiological underpinnings of network dysfunction and impaired interactions remain poorly understood. Recently, however, some theoretical hypotheses have been elaborated for the complex dynamics between large-scale neural systems. For example, Anticevic and colleagues<sup>95</sup> proposed a model for the synaptic mechanisms of altered DMN suppression and DMN-CEN interactions: the anti-correlation between CEN and DMN activities during task performance is derived from the reciprocal network interaction through net inhibitory long-range projections, which are related to disrupted NMDA conductance onto GABAergic interneurons. According to this model, local disinhibition induces hyperactivity of DMN-type microcircuitry and hyposensitivity to long-range suppressive inputs from task-activated, cognitive-related microcircuits—which precludes silencing the already high-firing DMN at task onset. The specific mechanisms of GABAergic/glutamatergic neural interaction, as well as their regulation on the brain network activity, need to be explored in future research.

Third, despite the strong evidence for the clinical effectiveness of psychotherapy in treating MDD, the neural underpinning of depression-specific psychotherapies remains unclear. Our framework may help to explore this issue. For instance, in cognitive-behavioral therapy, patients are given explicit instructions on how to regulate their negative thoughts and emotions, which may increase CEN activity and decrease DMN activity, and thereby enhance patients' ability to complete reflective processing successfully.<sup>137–139</sup> Moreover, mindfulness therapy, which highlights present-moment awareness and acceptance, may alter activity in the SN, especially anterior insular activity, by decreasing the incongruence between the outcome of associative processing and the individual's expectations.<sup>140,141</sup> Based on a meta-analysis, Ma<sup>124</sup> further proposed that antidepressant medication and cognitive-behavioral therapy have different neuropsychological mechanisms: the latter targets prefrontal function by increasing inhibitory executive control, whereas the former may act more directly on the network associated with abnormal emotion generation/experience. Furthermore, a recent review proposed that psychotherapy may facilitate recovery and plasticity at the brain network level after antidepressant drugs reactivate a window of juvenile-like plasticity in the adult cortex.<sup>142</sup> Ongoing composite research on cognitive vulnerability, treatment effects, and brain network-level plasticity is very promising.

Fourth, evidence shows some overlap of dysfunctional neural processing among different disorders. For instance, similar DMN abnormalities reflecting internally oriented attention and thought are found in both depression and schizophrenia.<sup>143</sup> Our diagnostic categories are heterogeneous and likely encompass multiple biologically distinct entities. Future work using the research domain criteria on brain system dysfunction may provide valuable insights into which patients demonstrate these network-level abnormalities and how those relate across diagnoses.

Finally, much work remains for relating network models explicitly to cognition and neural computation.<sup>144–146</sup> The intrinsic functional connectivity and network model undoubtedly provides a unique and powerful tool to provide insight into the organization of distributed association brain networks, especially as an organizing framework for characterizing biological substrates in mental disorders. Some methodological problems remain, however, in studying such networks—such as the sensitivity of functional connectivity MRI to head motion and physiological artifacts,<sup>147,148</sup> and the effect of global signal regression on detecting anti-correlation between networks.<sup>46,149</sup> Difficulties also exist with the definition of node/edge and the interpretation of network measures; for examples, as an indirect, relative measure of neural-activity fluctuations, functional connectivity MRI measures have no proven biological interpretation. Therefore, more studies are needed to promote the translation from the network properties to the realities of behavior and neurobiology.

In summary, a growing body of neuroimaging research reveals that cognitive vulnerability, the most generally accepted psychological risk factor for depression, is associated with neural functional abnormalities. Under a dual-processing framework, we integrated the MDD-related cognitive-vulnerability factors in the context of an intrinsic network and cross-network interaction perspective. Although the hypothesis presented in this review remains somewhat speculative, it provides a unique understanding of the link between in vivo brain measurements and cognitive vulnerability, and it enhances our insight into the biological underpinnings in the development, maintenance, and treatment of depression. The integrative framework suggests a paradigmatic shift in cognitive-vulnerability research and potentially informs the development of targeted interventions for MDD.

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